cl cont.

X is -O- or -S-;
and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.

REMARKS

Entry of the foregoing and still further reexamination and reconsideration of the subject application, as now amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

To begin, we maintain that the true scope and content of the prior art, the differences between the claimed invention and such prior art, and the level of ordinary skill in this art, have yet to be definitively addressed.

Thus, we reiterate that the scope and content of the prior art includes the U. S. Patents Nos. 4,242,334 and 4,377,575, both to Stache et al (copies submitted with applicant's Reply filed September 29, 1986). The '334 patent, it will be recalled, relates to certain corticoid 17-(alkyl carbonates) necessarily comprising, e.g., a reverse ester function, bonded strictly to a methylene bridge depending from a 20-keto group. The '575 patent features related corticoid 17-(alkyl carbonates), but wherein the methylene moiety is a terminal group, not a bridge, and is necessarily halogenated.

More importantly, though, it too is reiterated that these anti-inflammatory "carbonate" patents themselves point to, rather than detract from, the non-obviousness and hence

148

patentability of the instantly claimed compounds, and clearly establish that the prior art steroidal esters and carbonates are not equivalent. Again note the "steroids" case of In re Grunwell and Petrow, 203 U.S.P.Q. 1055.

Surely, it must be borne in mind that applicant's "soft drug" approach*/ is a marked departure from traditional drug design based on structure/activity relationships, and emphasizes the factor of safety over that of intrinsic activity. Indeed, the ways in which the toxic dose of a target compound may be reduced depend upon the alteration of the disposition of the drug in the body. Thus, through the prodrug approach, the compound may be modified so that it is inactive of itself, but once it reaches its site of action, it becomes activated and produces its therapeutic effect. Hence, the distribution of the target compound is modified to reduce its undesired interaction with sites of action other than where it is wanted. The toxicity of the target compound may be divided into its intrinsic toxicity, which is related to its intrinsic activity, and the toxicities of its metabolites which may be inactive, active, or reactive. The toxicity of the inactive metabolite is, of course, zero, but those of the others are not. The toxicity of the active metabolites is of the same order as the intrinsic toxicity of the drug itself, but the pharmacokinetic distribution is different and therefore uncontrollable. The toxicity of the reactive metabolites is of a different order, and is the most important to avoid. Reactive metabolites are known to

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*/ See pages 2 and 3, and the paragraph bridging pages 6 and 7, of applicant's specification.

combine with DNA and other critical cellular macromolecules to produce mutations, cancer, and cellular necrosis. Since reactive drug metabolites are products of a reaction with enzymatically produced active oxygen, the avoidance of this route of metabolism will reduce a large portion of the toxicity of the lead compound.

The present invention, geared to specific derivatives, e.g., of hydrocortisone, features derivatizing known endogenous inactive metabolites of, e.g., hydrocortisone, for example, 11β, 17α-dihydroxy-androst-4-ene-17β-carboxylic acid, or cortienic acid, with metabolically labile biofunctional carbonate moieties. Such modification as to form a soft drug, which would have the same order of potency but a much lower order of toxicity, is a marked departure from the use of ester groups (see the prior art already of record) which have been shown to be effective in producing highly active compounds for dermal application (i.e., the antithesis of the "soft" drug approach).

Moreover, it too would have been expected by those skilled in this art that the simple 17β-esters would be subjected to intramolecular group transfer of the acyl moiety to the 17β-position, forming a reactive mixed anhydride species. This is precisely the situation that the soft drug approach seeks to avoid. The likely candidates for reaction with this type of reactive intermediate, the plasma proteins, would then be made immunogenic and cause unwanted side effects in such manner. The systemic lupus which is seen in some cases of hypercortisolism is, in fact, attributed to

just such a mechanism. The cortisol is postulated to react with nucleophilic groups borne by the proteins.

Only applicant has shown that this problem could be solved by the use of a 17α-alkyl carbonate in place of the 17α-acyl, in a 17β-ester steroidal basic nucleus. Likely this is so because of the lower electrophilicity of the carbon in the carbonate, as opposed to the carbonyl carbon in the ester. A resonance interpretation makes this apparent.

And comparing the immediately aforesaid versus the carbonate and ester prior art, it is again submitted that the claimed subject matter is manifestly patentable thereover.

Primarily consider that the file history of the '575 Stache et al patent itself demonstrates that the corticoid carbonates and esters are not equivalent. A copy of this Serial No. 216,258 file history was also submitted with the September 29, 1986 Reply; again note the Stache et al Responses, and the Alpermann Declaration evidencing that indeed the carbonates and esters are not equivalent per In re Grunwell and Petrow, supra.

It too will be appreciated that the Stache et al carbonates actually teach away from applicant's specific 17α-carbonate-17β-carboxylates. The Stache et al compounds, as aforesaid, necessarily comprise a halogenated methyl group, or a methylene bridge at the 21-position. In fact, in the file history of the '334 patent (Serial No. 930,194, copy also submitted on September 29, 1986), it is explicitly recognized that 17-carbonate-21-hydroxy compounds (more akin to those of applicant) are unstable. Applicant's specific carbonates, however, are not only stable, but are even more

stable than the carboxylates. This flies in the face of the Stache teachings. Further, the inactive metabolites of applicant's claimed compounds are themselves more stable than the metabolites of the carboxylates. Also consider that the Stache et al metabolites are active (or do not form metabolites and, hence, remain active), rather than inactive. Inactive metabolites, to reiterate, are the very prerequisites of a soft drug, a concept conspicuously alien to the prior art.

The Examiner too must recognize that prior art essentially the same as that already of record herein, namely, Phillipps et al, Edwards and Sarett et al, was judged and found infirm vis-a-vis the carbonates, whether singly or in any possible combination thereof, during the prosecution of the Stache et al applications. See again the Stache et al file histories of record.

Next, further addressing the prior art of record and the outstanding Official Action, and while certainly not required as per In re Grunwell and petrow, supra, comparative data have already been presented demonstrating the patentable non-obviousness of the claimed compounds versus the compounds of Phillipps et al (1) and (2), in the effects on granulation tissue formation and thymus weight caused by implantation of cotton pellets in rats.

In this regard, the record Declaration of Dr. Kazuyuki Nakagawa is undeniably probative. As is apparent from Table 1 of this Declaration, the representative compounds of the two "primary" references effect significant

decrease in thymus weight, even at a very low dose of 10 or 30 μg/pellet.

On the other hand, the claimed compounds which correspond to the reference compounds tested in the Declaration do not effect such significant decrease in thymus weight at the same dosage level. Note the third compound in TABLE IV on page 41 of the Specification and the first compound in TABLE V-b on page 43 of the Specification.

In view of this, the two primary references, Phillipps et al (1) and (2) do not teach the unexpectedly low levels of systemic side effects of the claimed compounds, and certainly do not render the claimed invention obvious.

We also categorically dispute that Sarett et al teaches the "conventionality" of modifying hydroxy substituent with oxycarbonyloxy substituents at the 17α-position of the steroid nucleus.

In the first place, it is not understood how only one reference can show the "conventionality" of the oxycarbonyloxy modification. Surely, it cannot be said that Sarett et al "teaches" such modification to be conventional.

Furthermore, Sarett et al is only concerned with a completely different class of compounds. The compounds disclosed in Sarett et al are saturated and unsaturated 17α-hydroxy-2-keto-pregnane-17-carbonates which are markedly different from the claimed androstane derivatives, especially in the absence of a hydroxyl group at the 11-position and the presence of the group $-CO-CH_2-Y$ (Y=halo or H) at the 17β-position. Such pregnane derivatives, which are ketone derivatives, are wholly distinct from the claimed androstane

derivatives which comprise an ester function (i.e., having a $-CO-O-R_1$ group at the 17β-position).

From the viewpoint of pharmaceutical activity, the compounds of Sarett et al are disclosed to have progestational activity and to be valuable as esterus regulating agents. See Col. 1, lines 24 to 27 of the '675 patent. Such pharmaceutical activity is not even remotely akin to the anti-inflammatory activity possessed by the compounds of Phillipps et al (1) and (2) and by the claimed compounds.

Therefore, one skilled in the art would certainly not be motivated to modify the 17α-position of the compounds of Phillipps et al (1) and (2) with an oycarbonyloxy moiety. One skilled in the art could not predict what would happen when the alkanoyloxy group of the anti-inflammatory compounds of Phillipps et al is modified by the oxycarbonyloxy group "suggested" by Sarett et al to be responsible for a completely different and irrelevant pharmaceutical activity.

Furthermore, Sarett et al does not at all teach that such oxycarbonyloxy modification will result in a marked improvement in anti-inflammatory activity and concomitant marked decrease in systemic side effects.

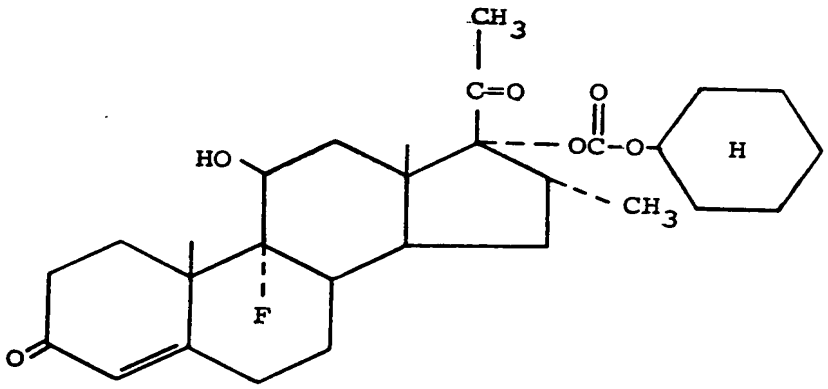
This has even been clarified. See again Experiment 2 of Dr. Nakagawa's record Declaration. From Table 2 of this particular Declaration, it will be seen that replacement of the alkanoyloxy group of the compounds of Phillipps et al by the oxycarbonyloxy group results in marked increases in the therapeutic indices. The therapeutic index of the compound of Ex. 7A-3 is about 26 times higher than that of the

corresponding compound of Phillipps et al, and the therapeutic index of the compound of Ex. 7A-12 is at least 10 times higher than that of the corresponding compound of Phillipps et al. This indicates that the oxycarbonyloxy replacement results in a significant increase in anti-inflammatory activity relative to lower systemic side effects. Such marked improvement is conspicuously absent from the teachings of Sarett et al and/or Phillipps et al (1) and (2).

In capsule summary, not even a scintilla of evidence has been adduced supporting the proposition that applicant's particular steroidal mixed esters/carbonates would even be prima facie obvious. In re Grabiak, 226 U.S.P.Q. 870; In re Grunwell and Petrow, supra.

More icing on the cake is provided by the attached second Declaration of Dr. Kazuyuki Nakagawa, specifically comparing the broad spectrum of prior art compounds (including those of the Stache et al patents which themselves relate to certain compounds of the type described in the ancillary Sarett et al reference).

Sarett et al discloses at columns 2 and 3 a compound designated 9α-fluoro-11β,17α-dihydroxy-16α-methyl-pregn-4-ene-3,20-dione 17-cyclohexyl carbonate which is represented by the formula



This type of compound is also within the ambit of the Stache et al patents.

Accordingly, Dr. Nakagawa has now compared this type of compound taught by the Sarett et al and Stache et al patents with a claimed compound. Compound (C) shown on page 3 of the second Nakagawa Declaration was selected as a representative compound per the Sarett et al and Stache et al patents. The claimed compound compared with Compound (C) above was Compound (A), also shown on page 3 of the second Nakagawa Declaration. Compound (A) and Compound (C) have identical substituents on the corresponding positions, except for the 17β-position. That is to say, Compound (C) of the Sarett et al and Stache et al patents has an ether group $-CO-CH_2Y$ at the 17β-position, whereas Compound (A) of the invention has an ester group $-CO-O-R_1$ at the same position. However, Compounds (A) and (C) have identical substituents at the other corresponding positions.

Furthermore, Compound (A) of the claimed invention was compared with a compound described by Phillipps et al 1 and 2, i.e., Compound (B) shown on page 3 of the second Nakagawa Declaration. Compound (B) of Phillipps et al and

Compound (A) of the invention have identical substituents on corresponding positions, except for the 17α-position (at which Compound (B) has a $-OCOR^3$ group, whereas Compound (A) of the invention has a carbonate group $-OCOOR_2$).

Thus, the claimed compounds have a carbonate group $-OCOOR_2$ per Sarett et al (and the Stache et al patents) at the 17α-position and an ester group $-CO-OR_1$ per Phillipps et al at the 17β-position. Such specific combination of 17-position substituents has been determined to be very important for achieving high anti-inflammatory activity, while at the same time reducing toxicity/undesirable side effects.

As will be seen from Table A on page 4 of the second Nakagawa Declaration, Compound (A) according to the invention has an unexpectedly higher therapeutic index compared with Compounds (B) and (C).

Table B on page 5 of the second Nakagawa Declaration reflects that the compound of the invention which has a $-OCO_2C_5H_{11}$ group at the 17α-position, i.e., Compound (D) shown on page 5 thereof, also has a high therapeutic index compared with Compound (B).

Such excellent therapeutic advantage imparted by the specific combination of the 17-position substituents according to the present invention is not even remotely akin to any concept disclosed or suggested by Sarett et al (or the Stache et al patents), Phillipps et al or Edwards.

According to the outstanding Official Action, Sarett et al teaches that modification at the 16 and 17 position substituents produces compounds with high activity.

Such teaching, however, is in fact conspicuously absent from Sarett et al. Sarett et al merely suggest that certain steroidal carbonates have progestational activity and are useful as esterus regulating agents. Such utility is profoundly remote from the anti-inflammatory activity possessed by applicant's claimed compounds. Sarett et al are totally silent as regards anti-inflammatory activity and low toxicity or side effects that characterizes the claimed compounds, and does not even allude to modification of the 17-position substituents with a view towards improving anti-inflammatory activity and at the same time lowering the side effects, i.e., for improving therapeutic index.

As is apparent from the test results relative to the Compound (C), merely having a carbonate group ($-OCOOR_2$) at the 17α-position (per Sarett et al or the Stache et al patents) does not provide an unexpectedly high therapeutic index. Similarly, as seen from the test results relative to Compound (B), merely having an ester group ($-CO-OR_1$) at the 17β-position (per Phillipps et al) also does not provide an unexpectedly high therapeutic index. Only when an ester group ($-CO-OR_1$) is present at the 17β-position and a carbonate group ($-OCOOR_2$) is simultaneously present at the 17α-position, will the resulting compounds display unexpectedly high therapeutic indices. These unexpected results are a marked departure from the state of this art. The claimed compounds profoundly differ from those of the prior art, exhibit therapeutic indices which could not be predicted therefrom, and are consummately patentable thereover.

We lastly emphasize, though, that the aforediscussed evidence of surprising and/or unexpected results is in reality an aside. It truly is unessential for a conclusion of non-obviousness on this record. In plain terms, the combination of references upon which the Examiner's §103 rejection is based, cannot be justified. There exists no logical reason apparent from positive, concrete evidence of record which justifies combining references featuring anti-inflammatory steroids with a reference featuring compounds having progestational activity that are valuable as esterus regulating agents. In re Stemniski, 170 U.S.P.Q. 343; In re Regel, Buchel & Plempel, 188 U.S.P.Q. 136. The prior art is itself sorely lacking in any suggestion whatsoever that the combination postulated by the Examiner would either be desirable or operative. In re Imperato, 179 U.S.P.Q. 730; In re Gruskin, 110 U.S.P.Q. 288; Ex parte Walker, 135 U.S.P.Q. 195.

It is submitted that only applicant's specification suggests any reason for combining the teachings of the prior art, but use of such suggestion is, of course, improper under the mandate of 35 U.S.C. §103. In re Shaffer, 108 U.S.P.Q. 326; In re Pye, 148 U.S.P.Q. 426; In re Wesslau, 147 U.S.P.Q. 391.

The prior art, in sum, contains absolutely no motivation to make applicant's claimed compounds. In re Taborsky, 183 U.S.P.Q. 50.

Request For Interview:

Upon consideration of all of the aforesaid, the Examiner is requested to telephone the undersigned, at (703) 836-6620, to schedule an interview whereat each topic above outlined can be more fully developed, if deemed at all necessary.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

Respectfully submitted,

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